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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,587	05/16/2001	Yoshiki Sasai	00766.000044.	1416

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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
06/24/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/855,587	SASAI ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15,18-21,23-75 and 80-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15,18-21,23-75 and 80-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 02/26/2010 have been fully considered.

Claims 1, 15, 18-21, 23-24, 25-73, 74-75, 80-90 are pending and under consideration. The amendment has been entered. Claims 2-14, 16-17, 22, 25-73, 76-79 are canceled.

Claim Rejections - 35 USC § 112/Necessitated by Amendment

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 15, 18-21, 23-24, 25-73, 74-75, 80-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The present claims have been amended to recite and encompass a method that has culturing an embryonic stem cell in vitro in the absence of retinoic acid and in the presence of a stroma cell without forming embryoid body, wherein the stroma cell is OP9 cell or PA6 cell. Claims have been amended to recite and encompass a method that has culturing for a time period from 1 to 14 days an embryonic stem cell in vitro in the absence of both retinoic acid and BMP4 and in the presence of a stroma cell forming embryoid body, wherein the stroma cell is OP9 cell or PA6 cell.

Literal support for these steps and what is accomplished by these steps cannot be found in the specification. More specifically, the culturing continuously the cell in vitro in the absence

of retinoic acid and in the presence of the stroma cell is OP9 cell or PA6 cell without forming embryoid body is affecting the embryonic stem cell to differentiate into the claimed neural cells cannot be found. The method steps in examples 1 or 14 of the specification, wherein EB5 embryonic stem cells cultured in the presence of PA6 stromal cells for 10 days exhibit dopaminergic marker, GABAnergic marker serotonergic marker or cholinergic marker cell specific markers so no support for culturing in the absence of retinoic acid as instantly claimed. In addition, the method steps of examples 1 or 14 in the specification provide no support for culturing an embryonic stem cell in vitro in the absence of both retinoic acid and BMP-4 and in the presence of OP9 cell or PA6 cell as instantly claimed in claim 81. It is noted that the Applicants fail to point to any specific support for the culturing of the cells in vitro in the absence of retinoic acid as discussed in the previous office action mailed on 9/30/2009, page 3.

MPEP 2163.06 notes "If new subject matter is added to the disclosure, whether it be in the abstract, the specification, or the drawings, the examiner should object to the introduction of new matter under 35 U.S.C. 132 or 251 as appropriate, and require applicant to cancel the new matter. If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981). The examiner should still consider the subject matter added to the claim in making rejections based on prior art since the new matter rejection may be overcome by applicant. In an instance in which the claims have not been amended, per se, but the specification has been amended to add new matter, a rejection of the claims under 35 U.S.C. 112, first paragraph should be made whenever any of the claim limitations are affected by the added material. When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to

determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claims 1, 15, 18-21, 23-24, 25-73, 74-75, 80-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for culturing a mouse embryonic stem cell in vitro in the presence of a stroma cell without forming embryoid body, wherein the stroma cell OP9 cell or PA6 cell, does not reasonably provide enablement for culturing a human embryonic stem cell in vitro in the presence of a stroma cell without forming embryoid body, wherein the stroma cell OP9 cell or PA6 cell, and wherein the embryonic stem cell is selected from the group consisting of (b) an embryonic stem cell established by culturing an early embryo produced by nuclear transplantation of he nucleus of a somatic cell; and (c) an embryonic stem cell in which a gene on the chromosome of the embryonic stem cell of (b) is modified using gene engineering. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention in scope with these claims.

The claims as amended embrace culturing a human embryonic stem cell in vitro in the absence of retinoic acid and in the presence of a stroma cell without forming embryoid body, wherein the embryonic stem cell is selected from the group consisting of (b) an embryonic stem cell established by culturing an early embryo produced by nuclear transplantation of he nucleus of a somatic cell; and (c) an embryonic stem cell in which a gene on the chromosome of the embryonic stem cell of (b) is modified using gene engineering.

The specification teaches co-culture of PA6 cells with the mouse EB5 cells in serum free medium and comparing the affect of the presence and absence of BMP4 in the serum free medium during the culturing/differentiation of the mouse ES cells (example 14). The

specification teaches the co-culture of PA6 cells with the mouse EB5 cells in serum free medium and after 8 days stained for the nestin neural specific marker and after 10 days stained for dopaminergic marker, cholinergic neuron marker, GABAnergic marker serotonergic a marker or dopaminergic marker (specification p. 93, example 1). However, the specification has failed to provide guidance for co-culturing human ES cells with OP9 stroma cells in the presence or absence of growth factors resulting in producing neural cells with neural surface markers. In addition, applicants failed to provide guidance for culturing a human embryonic stem cell in vitro in the absence of retinoic acid and in the presence of a stroma cell without forming embryoid body, wherein the embryonic stem cell is selected from the group consisting of (b) an embryonic stem cell established by culturing an early embryo produced by nuclear transplantation of he nucleus of a somatic cell; and (c) an embryonic stem cell in which a gene on the chromosome of the embryonic stem cell of (b) is modified using gene engineering resulting in producing a neural cell expressing a neural surface marker and or and wherein the human embryonic stem cell differentiates into a dopaminergic neuron, an acetylcholinergic neuron, a γ-aminobutyratergic neuron or a serotonergic neuron as instantly claimed.

Claims embrace a method step of culturing human embryonic stem cells in vitro in the presence of a stroma cell without forming embryoid body, wherein the stroma cell is OP9 or PA6 cell. It is noted that the claims embrace differentiating of a human embryonic stem cell is induced under any growth factors in vitro. The inventive concept in the instant application is the ability to direct the differentiation of human embryonic stem cells to preferentially yield a chosen neural cell type. The specification exemplifies a method wherein mouse embryonic stem cells are induced to differentiate into a neuron in presence of serum free medium and in the presence or absence of BMP-4 (see example 14). In the instant case, specification does not teach growth factor conditions for differentiation human ES cells under co-culture conditions in presence or

absence of BMP-4 and/or of any growth factor molecule. The art teaches that what requirements of growth factors are needed for differentiation of mouse ES cells are not applied to differentiation of human ES cells. The art teaches that the *in vitro* differentiation of human motor neuron from human embryonic stem cells requires specific signaling molecule and dependent upon the extent, time and selection of morphogens for induction under *in vitro* conditions. **Li et al** (Nat Biotechnol. 2005 Feb;23(2):215-21) that discloses retinoic acid action is required during neuroectoderm induction for motoneuron specification and suggests that stem cells have restricted capacity to generate region-specific projection neurons even at an early developmental stage (abstract, also page 217, col. 1, para. 2). Li et al further exemplified that hES cells also appear to be more sensitive to morphogens in motoneuron differentiation than are mouse ES cells. Li et al emphasize that ES cells need to be neutralized and then regionalized to progenitors before differentiation into specialized neurons and these processes are not simply linear but perhaps overlapping. Li et al show that both the Pax6- and Sox1-expressing neuroectodermal cells can differentiate into large neurons and express transcription factors, such as Islet1 and Lim3, that are associated with motoneuron development, but only neuroectodermal cells treated with retinoic acid at an early not a late stage express (emphasis added) a balanced level of class I and class II homeodomain genes, leading to the specification of spinal motoneurons. In the instant case, specification does not provide any guidance with respect to what growth factors are needed for differentiation of human ES cells not needed for differentiation of mouse ES cells. The guidance provided in the specification is limited to treatment of mouse ES cells in the presence or absence of BMP4, therefore, an artisan would have to perform undue experimentation to make and use the invention without any reasonable expectation of success. Absent of evidence to the contrary, it is not clear that absence or presence of BMP-4 would be functional in differentiating hES cell treated with or without BMP-4

at any stage of differentiation would yield a neuron cell type as embraced by the breadth of the claims. Given such importance of treatment of growth factors at specific stage of differentiation, particularly when taken with the lack of guidance in the specification for differentiating hES in presence of any growth factor, it would have required undue experimentation to establish the stage and importance of other signaling molecule and consequences of that product. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991)*. It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994)*, citing *In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991)*. An artisan would have to perform undue experimentation to determine the appropriate growth factors that would specifically differentiate hES cells in a human neuron that are a dopaminergic neuron, an acetylcholinergic neuron, a γ-aminobutyratergic neuron or a serotonergic neuron as instantly claimed.

Second, the art teaches that it is unpredictable to (a) having a human embryonic stem cell by culturing an early embryo produced by nuclear transplantation of the nucleus of a somatic cell and (b) an embryonic stem cell in which a gene on the chromosome of the embryonic stem cell (a) is modified using gen engineering. Although one might be able to isolate a particular cell type from an NT-produced mouse embryo, a NT-produced human embryo and a bioengineered human embryonic stem from a NT-produced human embryo is not found to be predictable. The instant invention is not enabling because the claims as written require that a human embryonic stem cell is derived from a human embryo produced nuclear transplantation, be able to differentiate into a neural cell in vitro, the state of the art of which is

unpredictable. For example, **Lerou et al,** (Blood Reviews, 19: 321–331, 2005) teaches theoretically, while generating ESC from somatic nuclear cell transfer embryos in mice is well established in 2004, a group of scientists from Korea reported deriving the first hESC line from a human blastocyst created using somatic cell nuclear transfer however, it remains to be seen whether mitochondrial DNA which would be oocyte derived (p 325, 1st column, 1st paragraph). Thus, the unpredictability in the claimed invention is to use these cells to engineer differentiated human ES cells into neural cells in vitro. The claims require the engineering of cells isolated from the embryo produced by nuclear transfer. However, as noted above, the state of the art teaches that the production of a NT-produced human embryo, as required by the claims, for the culture of human embryonic stem cells to differentiate into neural cells as instantly claimed would be unpredictable. The instant specification fails to provide teachings or guidance to address or overcome the above-noted unpredictability's that the state of the art teaches with regard to the generation of a NT-produced human embryo resulting in human embryonic stem to be cultured and differentiated into neural cells in vitro. As such, the instant specification fails to enable the invention.

The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of generation of a NT-produced human embryo resulting in human embryonic stem to be cultured and differentiated into neural cells in vitro raised by the state of the art. The instant specification does not provide guidance for growth factor conditions requirement needed for human ES cells not applied to mouse ES cells. Specifically the lack of the appropriate growth factors that would specifically differentiate hES cells in a human neuron that are a dopaminergic neuron, an acetylcholinergic neuron, a γ-aminobutyratergic neuron or a serotonergic neuron as instantly claimed.

Therefore, the skilled artisan would conclude that the state of art of generation of a NT-

produced human embryo resulting in human embryonic stem to be cultured and differentiated into neural cells in vitro by way of the claimed method is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for generation of a NT-produced human embryo resulting in human embryonic stem to be cultured and differentiated into neural cells in vitro without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the for generation of a NT-produced human embryo resulting in human embryonic stem to be cultured and differentiated into neural cells in vitro, the lack of direction or guidance provided by the specification for generation of a NT-produced human embryo resulting in human embryonic stem to be cultured and differentiated into neural cells in vitro, the absence of working examples that correlate to generation of a NT-produced human embryo resulting in human embryonic stem to be cultured and differentiated into neural cells in vitro, the undeveloped state of the art pertaining to generation of a NT-produced human embryo resulting in human embryonic stem to be cultured and differentiated into neural cells in vitro, and the breadth of the claims directed to all types of bioengineered human embryonic stem cells from NT-produced human embryo, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention. Therefore, the skilled artisan would conclude that the state of art of producing neural cells as instantly claimed is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for producing these cells without a reasonable expectation of success.

Applicants argue the claims have been amended to eliminate the issues of continuous culture and the issues of generating neural crest cell. The claims as currently amended stand

the issues of unpredictability as discussed above.

Claim Rejections - 35 USC § 102/103/Necessitated by Amendment

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 18, 20, 80-81 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over **Kuehn et al,** (Nature, 326: 295-298, 1987 (IDS) is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103/Necessitated by Amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 23, 81, 82-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Nakano et al,** (Science, 265: 1090-1101, 1994) in view of **Samarut et al** (US 6,114,168).

To the extent the instant claims read on a method requiring the active steps of culturing an embryonic stem cell in vitro in the absence of retinoic acid and in the presence of a stroma cell is OP9 the following rejection over the prior art is applicable.

Nakano et al teach the co-culture of mouse embryonic stem cells with the OP9 stroma cell for 1 to 14 days (p 1099 and figure 1). Nakano differs from the present invention for not teaching the absence of retinoic acid.

However, at the time of the instant invention **Samarut et al** (US 6,114,168) teaches the maintenance of primate stem cells on stromal cells. Samarut teaches the use of mouse STO cells as feeder cells (column 3) and specifically teaches to exclude retinoic acid from the culture media (abstract). Samarut teaches the absence of retinoic acid increases the number of totipotent embryogenic stem cells.

As such, because Samarut et al. teach that the absence of retinoic acid is functional equivalent, it would have been obvious for an artisan to use culture media without retinoic acid of mouse ES cells with OP9 cells to increase the number of totipotent embryonic stem cells in order to produce a cell expressing a neural surface marker. That is, it would have been a matter of design choice for an artisan to use media without retinoic acid to co-culture mouse ES cells with stroma OP9 cells to produce neural cells expressing neural surface markers.

The methods of Nakano/Samarut embrace the instant claims because there is not a step of growth factors in the pending claims to differentiate them from those set forth by Nakano/Samarut. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "*prima*

facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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